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## The correlation between insulin-like growth factor 1 (IGF-1) and novel adipocytokines in postmenopausal women: A population-based study

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### ABSTRACT

The adipocytokines and insulin-like growth factor 1 (IGF-1) are involved in insulin resistance, the cardiometabolic syndrome, and atherosclerosis. Therefore, investigating the relationship between circulating levels of the novel adipocytokines and IGF-1 is worthwhile. The correlation between IGF-1, visfatin, and omentin-1 has not been adequately investigated. In a population-based study, 324 postmenopausal women were randomly selected. Circulating IGF-1, visfatin, omentin-1, adiponectin, and high-sensitivity C-reactive protein (hs-CRP) levels were measured with the highly specific enzyme-linked immunosorbent assay method. In multiple regression analyses adjusted for alkaline phosphatase, osteocalcin, and hs-CRP, circulating IGF-1 was significantly correlated with visfatin levels (standardized  $\beta$  coefficient [ $\beta$ ] = 0.13, partial correlation coefficient [ $r$ ] = 0.12,  $p$  = 0.028). The significant positive correlation between serum IGF-1 and visfatin levels remained after additional adjustments for age and BMI ( $\beta$  = 0.12,  $r$  = 0.12,  $p$  = 0.025), metabolic syndrome ( $\beta$  = 0.13,  $r$  = 0.12,  $p$  = 0.021), and type 2 diabetes mellitus ( $\beta$  = 0.13,  $r$  = 0.12,  $p$  = 0.026). No significant correlations were found between IGF-1, adiponectin, and omentin-1. There is a significant correlation between serum IGF-1 and visfatin levels in postmenopausal women beyond metabolic syndrome, type 2 diabetes, bone formation markers, and hs-CRP levels. The observed correlation between higher circulating IGF-1 and the higher visfatin levels might be a physiological compensation and adaptation to protect against visfatin-induced proinflammatory effects.

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## Introduction

The adipocytokines expressed specifically and abundantly in adipose tissue influence many organ systems with important systemic interactions. Over the past few years, adipocytokines have been the focus of research on diabetes, obesity, and cardiovascular diseases because several classic and novel adipocytokines regulate metabolism and insulin resistance and contribute to chronic inflammation associated with metabolic syndrome and cardiometabolic disorders (1). Some adipocytokines such as adiponectin and omentin-1 are cardioprotective and counteract chronic low-grade inflammation and endothelial dysfunction (2).

Adiponectin has attracted much attention due to its antidiabetic, anti-inflammatory, and anti-atherogenic properties (3). Adiponectin is

negatively correlated with various obesity measures, as well as with insulin-resistance indices (4). Omentin-1 enhances insulin action and Akt phosphorylation (5), and omentin-1 is downregulated by elevated insulin and glucose levels (6). Omentin-1 also is inversely related to obesity and insulin resistance and positively correlated with adiponectin levels (7). Omentin-1 levels were lower in patients with metabolic syndrome than in controls (8).

However, several adipocytokines such as leptin, resistin, and visfatin may contribute in the pathogenesis of atherosclerosis (2). Visfatin (nicotinamide phosphoribosyltransferase (NAMPT) or pre-B-cell colony-enhancing factor 1) is secreted abundantly by the visceral fat in humans and mice and mimics the action of insulin (9). In vitro and in vivo studies have shown that visfatin may be involved in the

development and progression of atherosclerosis through cell proliferation, monocyte/macrophage activation and recruitment, vascular smooth muscle inflammation, and plaque destabilization (10). Human studies have shown inconsistent and conflicting results regarding associations between visfatin and the insulin-mimetic effect, insulin resistance, beta cell function impairment, adiposity, subcutaneous versus visceral fat distribution, and diabetes (11–13).

Insulin-like growth factor 1 (IGF-1) is a 7.6 kDa 70-amino-acid peptide, which is primarily synthesized in the liver in response to growth hormone. Accumulating evidence supports the regulatory roles of IGF-1 in proliferation, differentiation, metabolism, senescence, and apoptosis (14). The mitogen-activated protein kinase (MAPK) cascade and the phosphatidylinositol 3'-kinase (PI3K) pathway are involved in the mitogenic action and the metabolic and antiapoptotic signals of IGF-1 (15). In humans, an inverse association between circulating IGF-1 levels and atherosclerotic cardiovascular diseases as well as the prevalence of metabolic syndrome and its components has been observed (15–18).

Since the adipocytokines and IGF-1 are involved in insulin resistance, the cardiometabolic syndrome, and atherosclerosis (1–18), investigating the relationship between the circulating levels of novel adipocytokines and IGF-1 is worthwhile. This knowledge might provide useful insights into the pathophysiology of atherosclerosis and cardiometabolic risk.

There is little evidence regarding IGF-1 in relation to adiponectin levels, and the evidence is controversial. Positive correlation in obese nondiabetic women (19), negative association in type 2 diabetes mellitus (20), and no consistent association in postmenopausal women (21) were found between adiponectin and IGF-1 levels. The GH/IGF-1 cascade in relation to visfatin levels was investigated in patients with HIV (22), growth hormone deficiency (23), active acromegaly (24), retinopathy of prematurity (25), in relation to prenatal growth (26), and in human articular chondrocytes (27). However, whether or not serum IGF-1 levels are associated with omentin-1 has not yet been investigated. In the current study, we investigated the correlation between IGF-1 and adiponectin, omentin-1, and visfatin in a community-based study among postmenopausal Iranian women. To our knowledge, this is the

first population-based study that investigated the association among circulating IGF-1 concentrations, omentin-1, and visfatin levels.

## Methods

### *Community sampling and physical examinations*

The study design has been described previously (28). Briefly, the participants in the present study consisted of an age-stratified random sample of postmenopausal women, who participated in the extension of the Iranian Multicentral Osteoporosis Study (IMOS). The purpose of IMOS was to determine peak bone mass in healthy men and women. A total of 5201 participants were recruited from five major cities throughout the country in IMOS. According to the study protocol, 120 healthy men and women, aged 20–69 years in each age decade in every city should be randomly selected. We extended the study in order to include more postmenopausal women to determine postmenopausal osteoporosis in Bushehr (one of the five major cities). A total of 406 postmenopausal women were randomly selected from 13 clusters in the port city of Bushehr. However, 324 of the selected postmenopausal women had adequate aliquot of sera to measure the adipocytokines and IGF-1 levels.

All of the women, who were community dwelling and ambulatory, were asked to fast and to come to the survey center between 7:30 and 9:30 a.m. On arrival at the survey site, information regarding the participants' age, sex, marital status, and education was recorded. Further questions were asked about their smoking status, use of postmenopausal hormone replacement therapy, and any drugs taken for angina, as well as whether they had any history of hypertension, diabetes, or dyslipidemia.

The participants' blood pressure was assessed twice, via the right arm, after a 15-minute rest in the sitting seated position. A standard mercury sphygmomanometer was used. The women's heights and weights were measured using a stadiometer (heavy outer garments and shoes were removed first) and their body mass indexes (BMIs) were calculated.

### *Laboratory measurements*

Fasting blood samples were obtained from April 4 to September 22, 2006. Sera were then aliquoted

into microtubules and stored at  $-80^{\circ}\text{C}$  until analyzed. The analyses for glucose levels and lipid profile were carried out at the Persian Gulf Health Research Center on the day of blood collection using a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Glucose was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun Inc., Tehran, Iran). Serum total cholesterol and HDL cholesterol were measured using a cholesterol oxidase phenol aminoantipyrine, and triglycerides were measured using a glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum LDL cholesterol was calculated using the Friedewald formula; LDL cholesterol was not calculated when the triglyceride concentration was  $>400$  mg/dl.

All assays were performed according to the manufacturer's instruction; IGF-I levels were measured by DRG IGF-I 600 Enzyme Immunoassay Kit (DRG Instruments G mbH, Germany), and this kit is a solid-phase ELISA, based on the principle of competitive binding; osteocalcin was measured by N-MID Osteocalcin ELISA (Nordic Bioscience Diagnostics A/S, Herlev, Denmark), and this kit is based upon the application of two highly specific monoclonal antibodies against human osteocalcin; CrossLaps was measured by enzyme-linked immunosorbent assay (Nordic Bioscience Diagnostics A/S, Herlev, Denmark), the Serum CrossLaps® ELISA is based on two highly specific monoclonal antibodies against the amino acid sequence of EKAHD- $\beta$ -GGR, where the aspartic acid residue (D) is  $\beta$ -isomerized; alkaline phosphatase was measured by spectrophotometry using p-nitrophenylphosphate as substrate (Pars Azemon, Tehran, Iran); adiponectin was measured commercially by an available ELISA kits (Cat. No. AG-45A-0001EK-KI01; AdipoGen, Incheon, Korea), this assay is a sandwich Enzyme Linked-Immunoassay (ELISA) for quantitative determination of human adiponectin in biological fluids; omentin-1 was measured by omentin-1 (human) detection (ELISA kit [intelectin-1 (human) ELISA kit, Apotech Corporation, Switzerland]), the antibodies used in this kit are specific to the measurement of natural and recombinant human omentin-1; visfatin was measured commercially (Cat. No. V0523EK) by an available

enzyme-linked immunosorbent assay kit (AdipoGen, Seoul, Korea), this assay is a sandwich ELISA for quantitative determination of human Nampt in biological fluids; and C-reactive protein (CRP) was measured by CRP HS ELISA (DRG International), a highly sensitive (hs) CRP assay, the assay system utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the CRP molecule.

### Definitions

Using the American Diabetes Association's criteria, the existence of diabetes in a patient was defined either by a fasting plasma glucose level  $\geq 126$  mg/dL or by the use of antidiabetic measures (29). The metabolic syndrome was diagnosed with the criteria indicated by the NCEP-ATP III (30).

### Statistical analysis

The distribution of the data was controlled using the Kolmogorov-Smirnov test. A two-tailed t-test was used to compare the mean values across groups. We found that log transformation of adiponectin, visfatin, omentin-1, CrossLaps, osteocalcin, and IGF-1 gave a better fit to a Gaussian distribution. The geometric mean for those biochemical variables was defined as the arithmetic mean of the log-transformed data  $\pm$ SD, converted back to a base 10 number.

Pearson's correlation analysis was used to study the relationships between the log-transformed IGF-1 values and the anthropometric and biochemical variables. Partial correlation analysis was performed to assess the association between IGF-1 measurements and biochemical variables, with adjustment for age and weight.

Multiple linear regression models were used to assess the association between IGF-1 (as the dependent variable) and adipocytokines. The biochemical variables (alkaline phosphatase, osteocalcin, and hs-CRP) that showed significant correlations with IGF-1 levels were entered simultaneously in the standard linear regression models. The metabolic syndrome, type 2 diabetes mellitus, and BMI were considered as covariates in different multiple regression models.

A *p* value of less than 0.05 was accepted as significant. All statistical analyses were performed using PASW Statistics GradPack 18 (SPSS Inc., Chicago, IL).

## Results

The mean age (mean  $\pm$  SD) of the women was  $58.8 \pm 8.0$  years. The participants (324 postmenopausal women) were stratified into low (below or equal to the median) and high (above the median) serum IGF-1 groups. Table 1 shows the baseline characteristics of the study participants, stratified by IGF-1 groups. Women with high IGF-1 levels had significantly higher alkaline phosphatase and osteocalcin levels than women with low IGF-1 levels.

No significant correlations were found between IGF-1 and age, LDL cholesterol or HDL cholesterol, fasting glucose, triglyceride, systolic or diastolic blood pressure, weight, BMI, adiponectin, omentin-1, or visfatin in bivariate analyses. However, IGF-1 levels were significantly correlated with circulating alkaline phosphatase ( $r = 0.13$ ,  $p = 0.013$ ), osteocalcin ( $r = 0.12$ ,  $p = 0.017$ ), and hs-CRP ( $r = -0.13$ ,  $p = 0.012$ ) levels in the participants ( $p < 0.05$ ). These correlations persisted after further adjustment for age and weight. Of the participants, 79 (24.4%) had type

2 diabetes mellitus; and 228 women (70.4%) had metabolic syndrome (NCEP-ATP III criteria).

In multiple regression analyses adjusted for alkaline phosphatase, osteocalcin, and hs-CRP, circulating IGF-1 was significantly correlated with visfatin levels (standardized  $\beta$  coefficient [ $\beta$ ] = 0.13, partial correlation coefficient [ $r$ ] = 0.12,  $p = 0.028$ ). The significant positive correlation between serum IGF-1 and visfatin levels remained after additional adjustments for age and BMI ( $\beta = 0.12$ ,  $r = 0.12$ ,  $p = 0.025$ ), metabolic syndrome ( $\beta = 0.13$ ,  $r = 0.12$ ,  $p = 0.021$ ), and type 2 diabetes mellitus ( $\beta = 0.13$ ,  $r = 0.12$ ,  $p = 0.026$ ). However, no significant correlation between IGF-1 and adiponectin or omentin-1 was found in multiple regression models.

## Discussion

Abundant evidence supports the anti-inflammatory, antioxidant, and anti-atherosclerotic roles for IGF-1 (14–16). In addition, evidence that supports an interesting connection between visfatin and inflammation in cardiometabolic diseases is accumulating (10). Although we found no correlation between IGF-1 and visfatin levels in bivariate analyses, the positive significant correlation between these two markers was revealed after adjustment for chronic low-grade inflammation (hs-CRP) and bone formation biomarkers in multivariate regression models. The observed significant association between IGF-1 and visfatin levels in the current study raises this important question whether a unique pathophysiological mechanism exists behind the IGF-1 and visfatin correlation.

Unfortunately, studies on healthy adults in the medical literature about IGF-1 in relation to visfatin as an important proinflammatory marker are lacking. However, in vitro studies conducted by Olarescu et al. (24) revealed that IGF-1 promotes the inhibition of nicotinamide phosphoribosyltransferase (NAMPT)/visfatin expression during differentiation and in mature adipocytes. Therefore, the authors suggested that at least some of the known anti-atherosclerotic actions may be mediated through the inhibition of NAMPT/visfatin (24). In another in vitro study, Yammani and Loeser (27) investigated the role of NAMPT/visfatin in regulating IGF-1 function in human articular chondrocytes isolated from normal ankle cartilage. They found that the pretreatment of chondrocytes with NAMPT/visfatin inhibited IGF-

**Table 1.** The general characteristics, including blood pressure, anthropometric measurements, and the biochemical parameters of postmenopausal women, stratified by insulin-like growth factor 1 (IGF-1) levels below/equal or above.

	Serum IGF-1 $\leq$ median	Serum IGF-1 $>$ median
Age	$59.2 \pm 7.9$	$58.4 \pm 7.7$
Weight (kg)	$67.7 \pm 13.4$	$68.12 \pm 12.8$
Body mass index (kg/m <sup>2</sup> )	$28.1 \pm 4.9$	$28.5 \pm 5.0$
Systolic blood pressure (mmHg)	$127 \pm 19$	$124 \pm 20$
Diastolic blood pressure (mmHg)	$79 \pm 9$	$80 \pm 24$
Fasting blood glucose (mg/dl)	$119 \pm 58$	$112 \pm 47$
Triglyceride (mg/dl)	$119 \pm 89$	$179 \pm 102$
Total cholesterol (mg/dl)	$233 \pm 45$	$238 \pm 50$
HDL-cholesterol (mg/dl)	$40 \pm 10$	$42 \pm 11$
LDL-cholesterol (mg/dl)	$155 \pm 41$	$160 \pm 45$
Alkaline phosphatase (U/L)	$232 \pm 78$	$258 \pm 100^{**}$
Omentin (ng/mL)*	$11 \pm 3$	$12 \pm 2$
Adiponectin ( $\mu$ g/mL)*	$11 \pm 2$	$10 \pm 2$
Visfatin (ng/mL)*	$2.6 \pm 1.9$	$2.9 \pm 1.9$
CrossLaps (ng/mL)*	$1.8 \pm 1.6$	$1.6 \pm 1.7$
Osteocalcin (ng/mL)*	$10 \pm 1$	$12 \pm 2^{**}$
hs-CRP (mg/L)*	$1.9 \pm 2.8$	$1.6 \pm 2.5$

Values are mean  $\pm$  standard deviation

\*Geometric mean  $\pm$  standard deviation

\*\* $p < 0.05$



induced phosphorylation of signaling molecules, including insulin receptor substrate-1 and the Akt signaling pathway. They also demonstrated that the stimulation of chondrocytes with NAMPT/visfatin elicited a sustained phosphorylation of the extracellular signal-regulated kinase (ERK)/MAPK signaling pathway, independent of IGF-1 receptor activation. Although NAMPT/visfatin receptor for the activation of the ERK/MAPK pathway is unknown, these *in vitro* studies on human chondrocytes showed that NAMPT/visfatin-induced increased ERK/MAPK pathway results in decreased IGF-1 function (27).

Regarding the explanation for the observed positive relationship of visfatin (as an atherosclerotic adipocytokine) with IGF-1 (as an anti-atherosclerotic agent) in multivariate analysis among postmenopausal women, we hypothesized that the observed higher circulating IGF-1 in higher visfatin levels might be a physiological compensation and adaptation to protect against the NAMPT/visfatin-induced increased ERK/MAPK pathway that blocks IGF-1 function.

In the current population-based study, the regression models for IGF-1 in relation to circulating visfatin levels were adjusted for alkaline phosphatase, osteocalcin, and hs-CRP levels because we found that bone formation markers and hs-CRP levels were significantly correlated with IGF-1 levels in bivariate analyses. Overall, the significant correlation between IGF-1 and circulating visfatin was elucidated after adjustment for bone formation markers levels and chronic low-grade inflammation, as important determinants of circulating IGF-1 levels. The positive correlation between IGF-1 and bone formation markers and the inverse correlation between IGF-1 and CRP had been reported in previous studies (28,31).

Low circulating IGF-1 levels are associated with metabolic syndrome and its various components (18), risk of glucose intolerance, type 2 diabetes mellitus (15,32,33), and the increased prevalence of obesity (34). However, in the present study we demonstrated that IGF-1 was significantly correlated with visfatin levels when the logistic regression models were further adjusted for these confounding factors. Thus, our findings may confirm this concept that IGF-1 is linked with circulating visfatin beyond its relationship with metabolic syndrome, type 2 diabetes, and obesity measures.

In the current study, IGF-1 levels were not significantly correlated with circulating adiponectin. The medical literature is inconsistent in the correlation between IGF-1 and adiponectin and shows conflicting results. In 142 patients with heart failure, the log-transformed IGF-1 axis values had a negative correlation with the log-transformed serum adiponectin levels (35). Similarly, Kanazawa et al. (20) reported a significant inverse association between IGF-1 and adiponectin levels in Japanese men with type 2 diabetes independent of age, duration of diabetes, BMI, renal function, and HbA1c. The authors suggested IGF-1 might suppress serum adiponectin levels (20). However, a positive correlation between the IGF-1 z score and adiponectin was observed among obese nondiabetic women (19). This association remained significant even after adjustment for age, BMI, insulin sensitivity, and chronic inflammation indices (19). In agreement with our results, no consistent association between IGF-1 and adiponectin in healthy elderly male Lebanese (36) and among postmenopausal women (21) was reported. It seems that the conflicting results may arise because the studies were conducted in different categories of patients and serum levels of IGF-1 and this adipocytokine may be influenced by the accompanying pathological conditions (19).

The results of recent studies show sufficient evidence indicating that omentin-1 may be a good adipocytokine (19,20). Thus, omentin-1 may have a positive correlation with the IGF-1 level. However, we did not find a significant correlation between serum omentin-1 and IGF-1 values. Since there is no previously reported study regarding omentin-1 in relation to IGF-1, future studies are required to clarify and validate our results.

This study has several limitations. The present cross-sectional study does not allow for inferring causality from the observed correlation between circulating IGF-1 and visfatin in multivariate analyses. Determining the temporal sequence of any relationship between IGF-1 and this novel adipocytokine requires longitudinal studies. Since we assessed adipocytokines with single measurements, the changes in the adipocytokines over time were not reflected. Visfatin (9) and omentin-1 have insulin-mimetic properties (5); however, we did not adjust the regression models for measures of insulin resistance including HOMA-IR. The find-

ings from this postmenopausal cohort may not be generalized to other sex and age groups. Finally, to elucidate the underlying mechanism that regulates adipocytokines and IGF-1 cascade, additional inflammatory markers and cytokines should be measured simultaneously because the transcription and secretion of inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 visfatin are regulated by visfatin (37).

In conclusion, the current study demonstrated that postmenopausal women from the general population exhibit a significant correlation between circulating levels of IGF-1 and visfatin, independent of metabolic syndrome, type 2 diabetes, and obesity measures. Therefore, the findings of this first population-based study confirm the results of recent in vitro studies indicating that some anti-inflammatory and anti-atherosclerotic effects of IGF-1 may be counteracted by the visfatin effects.

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## Declaration of interest

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